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Chronic Pretreatment of ACEI Reduces No-Reflow in Patients with Acute Myocardial Infarction Treated with Primary Angioplasty

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Summary

Background: In animal models, pretreatment with angiotensin-converting enzyme inhibitor (ACEI) can reduce no-reflow. In the present study, we investigated whether pretreatment with ACEI may prevent no-reflow in patients who underwent primary coronary intervention for AMI.

Method and Results: A total of 259 consecutive patients who underwent primary angioplasty for a first AMI were studied. No-reflow was defined as a TIMI flow grade <3. The no-reflow phenomenon was found in 33 of 259 patients. There were no significant differences in clinical characteristics between the patients with and without ACEI pretreatment. However, the 47 patients receiving chronic ACEI treatment before admission had lower incidence of the no-reflow than those without it (4.2 and 14.6%, $p < 0.05$). Multivariable logistic regression analysis revealed that absence of ACEI pretreatment was a significant predictor of the no-reflow along with absence of preinfarction angina, complete occlusion of the culprit lesion, high-burden thrombus, ejection fraction on admission, number of Q-waves, absence of statin pretreatment, and anterior AMI.

Conclusion: Pretreatment with ACEI could preserve the microvascular integrity after acute myocardial infarction in humans.

Key words: myocardial infarction, reperfusion, angiotensin-converting enzyme inhibitor

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Primary percutaneous coronary intervention (PCI) is the preferred treatment for acute myocardial infarction (AMI). However, previous studies have shown that failure to achieve Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 after successful opening of the artery without angiographic evidence of mechanical obstruction is observed in 5% to 20% of patients treated with primary PCI and defined as the no-reflow phenomenon. The No-reflow phenomenon has been associated with severe myocardial injury, progressive left ventricular remodeling, congestive heart failure, and poor prognosis.[1,2] Pretreatment with angiotensin-converting enzyme inhibitor (ACEI) has been shown to be effective in attenuating no-reflow and reducing infarct size after AMI and reperfusion in the experimental models.[3,4] However, little is known about the effects of pretreatment with ACEI on reperfusion injury in patients with AMI. Therefore, in the present study, we investigated whether the chronic ACEI treatment could reduce the no-reflow in patients who underwent primary coronary intervention.

Methods

Study population

We studied 279 consecutive patients who underwent primary angioplasty for a first AMI between September 2001 and January 2005. The diagnosis of infarction

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was based on the chest pain, prolonged for $\geqslant$30 min, ST-segment elevation of $\geqslant$1 mm in at least two contiguous electrocardiography leads, and greater than twofold increase in serum creatine kinase levels. Cardiac symptoms lasting less than 30 min that occurred within 48 h before onset of infarction was defined as preinfarction angina. Twenty patients were excluded because of cardiogenic shock (8 patients) and thrombolytic therapy before angioplasty (12 patients). Therefore, the final study population consisted of 259 patients.

Study protocol

All patients received aspirin (300 mg) plus clopidigrel (300 mg) orally before coronary angiography. Glycoprotein IIb/IIIa inhibitors were not available in China. After intravenous heparin (100 U/kg) administration, coronary angiography was performed using the right femoral approach to determine culprit lesion and collateral channels. Collateral channels were graded according to the report by Rentrop[5] and good collateral flow was defined as grade 2 or 3. High-burden thrombus was indicated according to the report by Yip.[6] After intracoronary injection of nitroglycerin, we performed coronary intervention with angioplasty by using appropriate-sized balloon catheters. We repeated the angioplasty and implanted a stent. A clinical history of risk factors was determined from the detailed interview or medical records.

Electrocardiographic analysis

A repeat 12-lead ECG was obtained during and after each PCI procedure. The total ST-segment elevation (ΣST) was calculated in each electrocardiogram. To minimize the effect of the different number of leads involved, the sum was divided by the number of the leads presenting ST-segment elevation (ΣST index ΣSTI). Resolution of ST-segment elevation was defined as a decrease of at least 50% compared with the baseline ΣSTI. The ECGs were analyzed in a blinded fashion by an experienced cardiologist.

Angiographic analysis

The angiograms were reread as a single group, in chronological order, by experienced observers blinded to patient treatment. Coronary flow was graded according to the TIMIstudy criteria. No-reflow was defined as a TIMI flow < 3 in the absence of evident vessel dissection, obstruction, or distal vessel embolic cutoff.[7]

Statistics

Categorical data are presented as absolute values and percentages, whereas continuous data are reported as mean $\pm$SD. Continuous variables were compared by one-way analysis of variance (ANOVA) with Tukey-Kramer multiple comparison test. Comparisons of categorical variables were performed with the Fisher exact test. Univariable and multivariable logistic regression analyses were used to identify independent predictors for the no-reflow. A value of $p < 0.05$ (2-sided) was considered statistically significant.

Results

Patients characteristics

Among the 259 study patients (mean age, 60 ± 11), 207 patients (79.9%) were male. The median of the time from the symptomatic onset to coronary reperfusion was 5.5 ± 4.7 h. Hyperlipidemia was diagnosed in 139 patients. Hypertension was diagnosed in 128 patients, 79 patients had diabetes mellitus and 162 patients were current smokers (Table 1).

Forty-seven patients had chronically received ACEI before admission: 15 patients had received captopril (12.5–50 mg/day), 12 patients enalapril (5–10 mg/day), 20 patients fosinoprill (5–10 mg/day). There were no significant differences in baseline characteristics (such as age, gender, initial TIMI flow grade, time from symptom onset to restoration, heart rate on admission and baseline ΣSTI) between the patients with and without ACEI pretreatment except for hypertension history (Table 2). In addition, 43 patients had chronically received statin before admission: 20 patients had received pravastatin (20 mg/day), 16 patients simvastatin (20–40 mg/day), and 7 patients atrovastatin (10–20 mg/day). Only one patient had received both ACEI and statin before admission.

No-reflow phenomenon and pretreatment of ACEI

The 33 patients (12.7%) showed no-reflow. The no-reflow group had higher blood glucose on admission, prolonged symptom onset-reflow time, higher number of Q-waves, longer time to emergency room presentation, more initial TIMI 0 flow, more anterior wall infarction and lower ejection fraction (EF) than the reflow group (Table 1). Compared with the patients without ACEI, resolution of the ST-segment was more frequently observed in those with ACEI. The incidence of no reflow was significantly lower in patients with ACEI than in those without it (4.2% vs. 14.6%; $p < 0.05$) (Table 2).

Predictors of the no-reflow

Anterior wall infarction, preinfarction angina, initial TIMI 0 flow, ejection fraction on admission, number of Q-waves and absence of ACEI or statin pretreatment were the significant predictors in the univariable analysis.

TABLE 1 Clinical characteristics of the study patients

	All patients (n = 259)	Reflow (n = 226)	No-reflow (n = 33)	p-value
Age (years)	60 ± 11	58 ± 14	61 ± 13	0.2
Gender (male/female)	207/52	183/43	25/8	0.51
BMI (kg/m^2)	27 ± 1	28 ± 1	27 ± 1	0.72
CK on admission (IU/l)	868 ± 921	875 ± 986	869 ± 808	0.96
CK-MB on admission (IU/l)	89 ± 97	86 ± 85	91 ± 100	0.77
Blood glucose (mg/dL)	173 ± 61	152 ± 49	212 ± 68	0.001
Total cholesterol (mg/dL)	199 ± 45	201 ± 44	194 ± 47	0.38
Triglycerides (mg/dL)	113 ± 91	119 ± 99	100 ± 72	0.26
Risk factor (%)				
Hyperlipidaemia	139 (53.7)	122 (54.0)	17 (51.5)	0.71
Hypertension	158 (61)	112 (61.5)	19 (57.6)	0.39
Diabetes mellitus	79 (30.5)	69 (30.5)	10 (30.3)	0.87
Smoking	162 (62.5)	142 (62.8)	20 (60.6)	0.57
Symptom onset-reflow time (h)	5.5 ± 4.7	5.1 ± 4.9	6.7 ± 4.1	0.008
Preinfarction angina, n (%)	145 (56.0)	135 (59.7)	10 (30.3)	0.002
EF on admission (%)	47 ± 11	49 ± 13	40 ± 10	0.004
Hemodynamic data on admission				
HR (b/min)	83 ± 12	83 ± 13	85 ± 12	0.24
SBP (mmHg)	138 ± 27	136 ± 29	141 ± 23	0.34
Anterior wall infarction, n (%)	148 (57.1)	121 (53.6)	27 (83.1)	0.0002
High-burden thrombus, n (%)	108 (41.7)	78 (34.5)	30 (90.9)	0.0001
Initial TIMI flow grade 0 (%)	76.7	70.1	89.8	0.005
Good collaterals, n (%)	66 (25.5)	57 (25.2)	9 (27.3)	0.57
Number of Q-waves	3.5 ± 1.2	1.9 ± 1.7	3.4 ± 1.6	0.009
Baseline ΣSTI (mV)	0.34 ± 0.14	0.36 ± 0.16	0.31 ± 0.12	0.81
Medication before AMI				
ACEI pretreatment, n (%)	47 (18.1)	45 (19.9)	2 (6.1)	0.007
Statin pretreatment, n (%)	43 (24.3)	41 (18.1)	2 (6.1)	0.008
β-blocker pretreatment, n (%)	20 (7.7)	18 (7.9)	2 (6.1)	0.26
Aspirin pretreatment, n (%)	96 (37.1)	85 (37.6)	11 (33.3)	0.42

Abbreviations: *p values for the differences between reflow and no reflow. Data are presented as the mean value ±SD or number or percentage of patients.CK-MB = creatinine kinase,
EF = ejection fraction, HR = heart rate; SBP = systolic blood pressure, TIMI = Thrombolysis In Myocardial Infarction, AMI = acute myocardial infarction, ACEI = angiotensin-converting enzyme inhibitor, BMI = body mass index; ΣSTI = ΣST index.

Then, we performed multivariable logistic regression analysis using these parameters. The absence of ACEI pretreatment was an independent predictor of the no-reflow along with anterior wall infarction, high-burden thrombus, lack of preinfarction angina, ejection fraction on admission, initial TIMI 0 flow, absence of statin pretreatment and number of Q-waves (Table 3).

Discussion

A large body of evidence has accumulated over the past two decades to support the notion that angiotensin II through its AT1 receptor mediates a large array of biologic activity. Taken together, such effects promote atherosclerosis and progressive cardiac remodeling. The view is further supported by the protection afforded by ACEI in patients with cardiovascular disease http://www.jasn.org/cgi/content/full/15/1_suppl/S71-R8-136463http://www.jasn.org/cgi/content/full/15/1_suppl/S71-R9-136463http://www.jasn.org/cgi/content/full/15/1_suppl/S71-R11-136463http://www.jasn.org/cgi/content/full/15/1_suppl/S71-R12-136463http://www.jasn.org/cgi/content/full/15/1_suppl/S71-R13-136463. Although the animal experimental studies had demonstrated that ACEI reduced reperfusion injure, its effects on myocardial no-reflow in patients is unknown.

Incidence of no-reflow

Failure to achieve normal flow is increasingly recognized as primary PCI has become a widely popular mode of reperfusion for patients with AMI. The present study showed that the incidence of TIMI $\leqslant$2 flow is 12.7%, occurring in 33 of 259 patients undergoing primary PCI, which was consistent with the previous reports.[8] However, the actual incidence of TIMI $\leqslant$2 flow might be higher than that observed in the present study since ACEI

TABLE 2 Clinical characteristics of patients with or without ACEI

	With ACEI n = 47	Without ACEI n = 212	p-value
Age (years)	60 ± 11	60 ± 14	0.5
Gender (male/female)	71/16	138/34	0.21
BMI (kg/m^2)	27 ± 2	28 ± 3	0.72
CK on admission (IU/l)	901 ± 923	894 ± 901	0.84
CK-MB on admission (IU/l)	89 ± 76	90 ± 93	0.87
no-reflow, n (%)	2 (4.2)	31 (14.6)	<0.05
ST-segment Resolution, n (%)	43 (91.5)	153 (72.2)	<0.05
Blood glucose (mg/dL)	178 ± 59	182 ± 68	0.31
Total cholesterol (mg/dL)	198 ± 43	196 ± 52	0.47
Triglycerides (mg/dL)	107 ± 98	101 ± 78	0.56
Risk factor n,(%)			
Hyperlipidaemia	25 (53.2)	114 (53.8)	0.53
Hypertension	46 (97.9)	112 (52.8)	0.001
Diabetes mellitus	15 (31.9)	64 (30.2)	0.31
Smoking	28 (60.0)	134 (63.2)	0.17
Symptom onset-reflow time (h)	5.6 ± 4.3	5.9 ± 5.2	0.41
Preinfarction angina, n (%)	26 (55.3)	119 (56.1)	0.29
EF on admission (%)	47 ± 17	48 ± 14	0.36
Hemodynamic data on admission			
HR (b/min)	86 ± 15	83 ± 13	0.27
SBP (mmHg)	131 ± 31	136 ± 26	0.41
Anterior wall infarction, n (%)	25 (53.2)	123 (58.0)	0.19
High-burden thrombus, n (%)	20 (42.5)	88 (41.5)	0.87
Initial TIMI flow grade 0 (%)	78.1	79.8	0.53
Good collaterals, n (%)	14 (29.8)	52 (24.5)	0.47
Number of Q-waves	2.3 ± 2.1	2.6 ± 2.4	0.13
Baseline ΣSTI (mV)	0.34 ± 0.12	0.35 ± 0.16	0.76
Medication before AMI			
Statin pretreatment, n (%)	7 (14.3)	36 (16.9)	0.11
β-blocker pretreatment, n (%)	3 (6.4)	17 (8.0)	0.22
Aspirin pretreatment, n (%)	17 (36.2)	79 (37.3)	0.49

Abbreviations: *p values for the differences between the patients with or without ACEI = angiotensin-converting enzyme inhibitor. Data are presented as the mean value ±SD or number or percentage of patients. EF = ejection fraction HR = heart rate, SBP = systolic blood pressure, BMI = body mass index, TIMI = Thrombolysis In Myocardial Infarction and ΣSTI = ΣST index, AMI = acute myocardial infarction.

TABLE 3 Multivariable predictors of the no-reflow

	p	OR	(95%CI)
Anterior wall infarction	0.02	4.86	(1.23–19.19)
High-burden thrombus	0.004	2.76	(1.81–5.12)
Lack of preinfarction angina	0.03	3.54	(1.96–5.37)
Ejection fraction on admission	0.01	1.72	(1.25–2.71)
Initial TIMI flow grade 0	0.001	3.12	(1.91–5.13)
Number of Q-waves	0.004	1.56	(1.34–2.95)
Absence of ACEI pretreatment	0.02	1.06	(1.01–1.56)
Absence of Statin pretreatment	0.014	1.7	(1.16–2.98)

Abbreviations: OR, odds ratio; CI, confidence interval; TIMI, Thrombolysis In Myocardial Infarction; ACEI, angiotensin-converting enzyme inhibitor.

could reduce no-reflow. The gold standard for the assessment of the no-reflow phenomenon may be represented by myocardial contrast echocardiography after revascularization. However, myocardial contrast echocardiography cannot be routinely performed in our hospital. We used the TIMI flow grade, which is a highly specific, although not a sensitive tool to detect no-reflow, and thus, were also able to assess no-reflow.

ACEI and no-reflow

The present study demonstrated that the patients receiving chronic ACEI pretreatment had lower incidence of the no-reflow than those without ACEI. Multivariable logistic analysis revealed that ACEI pretreatment was an independent predictor for the no-reflow. The results indicated that ACEI could reduce no-reflow in humans, which is consistent with the experimental report

of Podesser. Podesser[3] demonstrated that angiotensin-converting enzyme (ACE) inhibition quinaprilat during cardioplegic arrest improves coronary perfusion in failing rat hearts. Our experimental study[4] also showed that ACE inhibitor fosinopril reduced the area of no-reflow assessed by both myocardial contrast echocardiography and pathological means in a miniswine model of acute myocardial infarction and reperfusion. The proposed mechanism of the no-reflow phenomenon after primary angioplasty is multifactorial, including endothelial damage, microvascular spasm, tissue edema, microembolization of thrombotic material, and plaque fragments. These factors determine a damage to the microcirculation during both the ischemic and the reperfusion phases. The precised mechanism, by which ACEI is beneficial in the reduction of the no-reflow, remains unclear. Several studies demonstrated that endothelial dysfunction could be a cause of the no-reflow after infarction.[9] ACEI has been shown to be effective in improving endothelial function.[10] Therefore, restoring of endothelial dysfunction with ACEI might be associated with the prevention of the no-reflow. In addition, ACEI limits the vasoconstriction by blocking the conversion of angiotensin I to angiotensin II and preventing the degradation of bradykinin into inactive peptides.[11] ACEI has also favorable effects on platelet activity,[12] thrombosis[13] and plaque stability.[14] These pleiotropic effects could also contribute to the preservation of microvascular function during ischemia and reperfusion.

Predictors of no-reflow

In our study, although univariate analysis revealed several clinical factors to be associated with TIMI $\leqslant$2 flow, multivariate analysis showed that the absence of pre-infarction angina, number of Q-waves, initial TIMI 0 flow, high-burden thrombus, anterior wall infarction and left ventricular ejection fraction (LVEF) <50% would be associated independently with the increased risk of TIMI $\leqslant$2 final flow. The results were consistent with previous studies evaluated predictors of TIMI $\leqslant$2 in patients with acute ST segment elevation myocardial infarction (STEMI) undergoing primary PCI.[6,15] Our study also demonstrated that statin was also an independent predictor for the no-reflow, which was consistent with the report of Iwakura.[16]

Limitation of the study

As a single-center observational study, some biases might be inevitable in the present study. Because wall motion score (WMS) was not routinely measured in our hospital, we did not know the size of the risk area. However, previous studies have identified greater size of the risk area is closely related to the no-reflow phenomenon.[15] The doses of ACEI in the study may be lower than the maximal recommended doses. This may lead to an underestimation of the effect of ACEI on no-reflow. Therefore, higher dose of ACEI could be more effective in reducing no-reflow.

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